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14. ABSTRACT Fragile X (FX) syndrome causes behavioral disturbances such as labile mood, anxiety, hyperactivity, and aberrant behavioral responses to stress. Affected males may suffer from learning disabilities, attention deficit disorders, mental retardation, or autism spectrum disorders. We seek to address the most effective methods of treatment (pharmacological and behavioral) for the symptoms and behavioral problems associated with FX syndrome. During the past year, we have established a comprehensive FX syndrome clinic and we continue to refine our treatment protocol. Collaborative relationships have been established with genetics, speech/language, psychiatry, ophthalmology and dental so that families can obtain these services from specific professionals with an interest in FX syndrome. School liaison services for school aged youth with FX syndrome have been established. Community education programs, in the form of a website, a parent advisory group, and announcements have been established. We continue to refine our database to track the frequency of the disease and specific symptoms with the goal of guiding future treatment through evidence based medicine.					
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REPORT: DAMD 17-03-1-0057
Pharmacological and Non-pharmacological Methods of Treatment
of Fragile X Syndrome

INTRODUCTION:

The Child Development Unit, Center for Neurosciences, and Division of Genetics of the Children's Hospital of Pittsburgh (CHP) are seeking to address the most effective methods of treatment – both pharmacological and non-pharmacological -- for the symptoms and behavioral problems associated with Fragile X (FX) syndrome.

This program will feature the recruitment of children with this disorder to conduct physiological and behavioral testing, with the goal of identifying effective interventions.

A local established registry will supply data on the behavioral phenotype of children with FX syndrome for future basic and clinical research as well as establishing best practice models for clinical care.

This program will establish a basic research program including development of genetically engineered mouse and primate models of the syndrome to determine the mechanism of, and potential novel treatments for symptoms of FX syndrome.

STATEMENT OF HYPOTHESIS

FX syndrome causes behavioral disturbances such as labile mood, anxiety states, hyperactivity, and aberrant behavioral responses to stress. Affected males may suffer learning disabilities, attention deficit disorders, mental retardation, and autism spectrum disorder. The Child Development Unit, Center for Neurosciences, and Division of Genetics at the Children's Hospital of Pittsburgh (CHP) now seek to address the most effective methods of treatment – both pharmacological and non-pharmacological – for optimal management of the symptoms and behavioral problems associated with FX syndrome. This initiative features the recruitment of children with this disorder to conduct physiological and behavioral testing, with the goal of identifying effective interventions. Finally, this initiative will establish a basic research program including development of genetically engineered mouse and primate models of the syndrome to determine the mechanism of, and potential novel treatments for symptoms of FX syndrome. Because the behavioral symptoms occurring in youth with FX syndrome also occur commonly in non-FX subjects and may affect the behavioral responses to stressful conditions, the overall program will have an impact on military personnel as well as children and families affected by FX syndrome.

OBJECTIVES

1. To establish a clinical center for diagnosis and treatment of individuals with FX syndrome, full, pre-mutation and intermediate alleles.

2. Provide community service and professional education about FX syndrome
3. To develop a registry and for FX patients and their families and to get approval for a sleep study.
4. To establish a basic research laboratory dedicated to studies on the pathobiology of neurobehavioral disturbances in FX syndrome, with a particular focus on new genetically engineered animal models of the syndrome

ACCOMPLISHMENTS (Year 2/28/06 – 2/28/07)

Objective 1: To establish a clinical center for diagnosis and treatment of individuals with FX syndrome

- Dr. Robert Noll and Rebecca Kronk have established a monthly Fragile X Center clinic. We are currently available to see all patients in the region with FX syndrome, full pre-mutation, and intermediate alleles and their families for comprehensive care visits when they request a visit. Access to our clinic for new patients with Fragile X is excellent (under 14 days).
- Dr. Dena Hofkosh serves as clinical medical consultant and is available as needed during the monthly Fragile X Center session.
- Paula Ciliberti, MA serves as Project Specialist and Family Liaison for the Fragile X Center. Her role is to support the mission of the center by focusing on 4 major areas of responsibility: promotion of the Center; support of clinical functions and clinical staff as well as families seen within the Center; development of Center activities; and administrative support. As Project Specialist Ms. Ciliberti helps to identify, support, and coordinate new endeavors that will promote the growth and development of the Center.
- We are increasing the number of children being referred to the Center through continued outreach efforts towards primary care physicians in the tri-state area.
 - Dr. Randi Hagerman's Grand Rounds in December, 2005, has been archived and made accessible on the Children's Hospital Fragile X Website for professionals as well as families locally, regionally, and nationally.
 - The Fragile X Center brochure, developed to increase awareness of the incidence of Fragile X syndrome and provide information about the Center and the services provided, is being distributed routinely to specialty departments within Children's Hospital, parents, caregivers, schools, community agencies, and others involved with children who may be at risk for Fragile X syndrome.
 - Phone calls, approximately 30 per month, coming to the Center from individual providers and families, regarding appropriate diagnostic testing and referrals are being promptly addressed by the coordinator of the Fragile X Center.

- In collaboration with CHP Public and Government Affairs, we maintain and update the CHP FX Center website <http://www.chp.edu/fragilex>. This website provides access to information about the Center and provides links to other local and national resources.
 - The Fragile X Parent Handbook, available both in a hard copy binder format as well as an e-version on-line on the CHP Fragile X Center website, is made available to families as well as other medical providers of children with Fragile X. A survey has been developed to gather data on the usefulness of this information provided as well as well as to gather information about the delivery of services to patients with Fragile X and their families.
 - In January 2006, Dr. Robert Noll spoke to CCP about the Fragile X Center and available services. Dr. Noll actively maintains this relationship with CCP.
- Dr. Robert Noll and Rebecca Kronk, CRNP have continued to establish relationships and communication with the National Fragile X Foundation, FRAXA Research, the MIND Institute, and the University of NC Durham Fragile X Center.

The FX Foundation was a co sponsor for the Fragile X Center Conference, *New Frontiers in Fragile X*, held December, 2006. The FX Foundation provided an electronic mailing “blast” to nearly 900 members within a 90 mile radius of Pittsburgh. This mailing announced our Conference and included an attached PDF with registration information.

Persons calling the National FX Foundation to find resources in Western Pennsylvania or the surrounding areas are provided information about the CHP Fragile X Center

- Our multi disciplinary provider network representing Genetics, Speech/Language, Ophthalmology, Dental, and Psychiatry, continues to function effectively. This group, comprised of dedicated specialists, both within CHP and UPMC, is committed to providing improved access to appropriate and necessary healthcare follow up for Fragile X patients. This provider network has offered a professional, efficient, and seamless approach to referrals for patients seen in the Center.
- We have contracted with Digital Miracles to build a database to provide the means for tracking Fragile X patients seen in the Fragile X Center. The database is intended to be used for actual patient care evaluations as well as for research. The Fragile X Center has seen significant growth since its inception. From June 2004 until February 2007 the number of children followed in the Fragile X Center, who have been diagnosed with Fragile X, Full, Premutation, and Intermediate, has grown significantly. In 2004

fourteen (14) children were followed. That number has increased to forty-two (42) in 2007. Having tripled in growth, and expecting this growth to continue, this database will provide us with a secure and more robust means of entering and tracking demographic, clinical, neurocognitive, behavioral, and research data. It will provide us with a means for tracking Fragile X patients seen in the Center both during and post treatment. The system is intended for actual patient care and evaluation as well as for research. This database will enable us to extract data for reporting or research purposes and will guide future treatment through evidence based medicine.

- We have established a community education program for FX syndrome. FX clinic interdisciplinary team members provide information to the quarterly newsletter about research, tips on behavioral management, and information about upcoming educational events such as web casts. A set of educational materials, donated to the FX clinic at CHP by the National FX Foundation, forms the foundation for our developing lending library. This library is available to FX clinic interdisciplinary team members and families of children seen in the clinic.
- Ongoing Goals
 - Expand number of patients and families followed by the Fragile X Center of CHP. We tripled our numbers in the past 3 years and we will continue to add patients exponentially.
 - Strengthen and expand our multi-disciplinary provider network to surrounding regions, including West Virginia and Ohio.
 - Utilize database information to create products for publication and guide clinical practice decisions and research.
 - Complete our ongoing sleep research project.

Objective 2: Provide community service and professional education about FX syndrome

Nationally

- In July 2006, Dr. Robert Noll, Rebecca Kronk, CRNP, and Paula Ciliberti, MA attended the **10th International Fragile X Conference in Atlanta, Georgia** along with nearly 1000 parents and professionals. Extensive networking that began with the 9th International Conference 2 years prior has resulted in solid working relationships at the local, state, and national level. During the five-day event, staff from the Fragile X Center were participants in the Conference along with individuals from 45 states plus the District of Columbia and Puerto Rico as well as 60 international conference participants representing 20 countries.
- During the five-day event, the Fragile X Center of Pittsburgh had one of 16 exhibit tables providing an opportunity for FX staff to share with interested conference participants what is going on with the Fragile X Center of Pittsburgh both from a clinical as well as a research perspective.

- Rebecca Kronk, CRNP, Clinical Coordinator of the Fragile X Center and Dr. Robert Noll, Director of the Fragile X Center represented the Center in a panel discussion that featured 12 Fragile X clinics at the International Fragile X Conference in Atlanta, July 2006. The panel provided a historical perspective of the 12 Fragile X clinics in the United States, introduced the audience to representatives from the clinics, and solicited input from families regarding services and resources they would like to see offered in the clinics. This panel discussion was germane to strategizing and forming a Fragile X Network Consortium, a group committed to determining the best way to organize, coordinate, collaborate and share knowledge and information of organizational, administrative and clinic structures, effective interventions, and the facilitation of collaborative research efforts.
- December, 2006, Dr. Michael Tranfaglia, Medical Director of FRAXA Research Foundation was a Guest Presenter at the Fragile X Center's Conference, *New Frontiers in Fragile X*. He offered the continued support of FRAXA as well as his own support of the establishment of the clinic.
- February 2007 Dr. Robert Noll and Becky Kronk traveled to St. Louis where they met with representatives from 12 other Fragile X Centers from the US and Canada for the first meeting of the Fragile X Clinic Consortium. The group met to continue the efforts begun in Atlanta, in July 2006, to determine the best way that the Fragile X clinics in the US and Canada can organize, coordinate, and collaborate. The group focused on the development of a shared knowledge base of organizational, administrative and clinic funding structures that will assist current and future clinics in becoming more effective and efficient; the development of a shared knowledge base of effective interventions; and the establishment of a structure for facilitating collaborative research for efforts, including drug trials.

Locally /Regionally

- Meetings with parents, four over the past year, have continued to discuss how the FX Center might better address the needs and concerns they have for their children. This collaborative working relationship with parents of children with Fragile X continually provides helpful input allowing us to better address current and ongoing concerns.
- The Fragile X Center developed a primary care physician packet of information which included the CHP FX clinic brochure; information about the recommended lab protocol for diagnostic testing when there is a suspicion of FX syndrome; and the American Academy of Pediatric Practice Guidelines of Care for patients with FX syndrome. This packet was distributed by CHP Public and Government Affairs regionally to 3500 primary care physicians and well as 1250 school psychologists statewide. The purpose of this mass mailing was to increase awareness of the primary care physician of the frequency and incidence of FX

syndrome within their practice; inform them about current updates on FX syndrome; and provide information about services offered to families through our center and the collaborating interdisciplinary team members.

- Dr. Robert B. Noll, Rebecca Kronk, and Paula Ciliberti attended the Biennial Fragile X Gala, *the X Ball*, held May 11, 2006 in Pittsburgh. The Gala, sponsored by FRAXA, Fragile X Research Foundation also recognized and celebrated the opening of the Fragile X Center. The Fragile X Center benefited by the increased awareness of our Center that ultimately resulted in a donation from the Fragile X Research Foundation from the proceeds of the Gala as well as a substantial donation from a private donor. The donated funds will largely be directed to research efforts.
- Paula Ciliberti, Project Specialist & Family Liaison, represented the Fragile X Center where the Center had one of 18 display tables offering information about their services. This mini conference was sponsored by the Allegheny County Offices of Mental Retardation/Developmental Disabilities and the Office of Aging. The purpose of the conference was to educate case managers about available services and the way to access these services as well as other community resources and services.

The Fragile X Center display offered their brochure and other informational handouts about the Center and the services provided. This venue offered an excellent opportunity to show the linkages between children with Fragile X and the many symptoms, the rates in adults, issues for young women, and issues for the elderly i.e. FXTAS

- The Fragile X Center sponsored a one-day conference, *New Frontiers in Fragile X*. The Conference focused on current discoveries and developments affecting the clinical presentation of the full and premutation of Fragile X syndrome, provided the audience with an overview of genetic mechanisms, illustrated how research advances can improve treatment and counseling for family members with Fragile X, and examined the benefits and challenges associated with newborn screening for Fragile X syndrome.

The primary objective of this conference was to provide state of the art information about Fragile X syndrome to families and professionals, both in the clinical and scientific community including primary care physicians, nurses, researchers, psychologists, and genetic counselors with the intent for participants to integrate the information to enhance care, treatment, education, and counseling as it effects individuals with Fragile X.

- Dr. Noll and Becky Kronk provided a training session, which focused on Fragile X, to The University, Community, Leaders, and Individuals with Disabilities (UCLID) Center. UCLID is an Interdisciplinary Training Program for graduate and doctoral students and post-doctoral fellows in Neurodevelopmental

Disabilities funded by the Maternal Child Health Bureau, U.S. Department of Education and United Way of Allegheny County. The UCLID Center is one of 35 [Leadership Education in Neurodevelopmental and Related Disabilities](#) (LEND) Programs in 29 states. Dr. Robert Noll is also the Director of the University of Pittsburgh Leadership Education in Neurodevelopmental and Related Disabilities (LEND) program. UCLID trains fellows (three this year) and graduate students (6 this year) to become leaders in the field of developmental disabilities. Dr. Noll is expanding the training of graduate and doctoral students to include interdisciplinary care of children with chronic illnesses and neurodevelopmental disabilities.

Collaborative educational and training efforts between the Fragile X Center and UCLID have included the local Fragile X Conference, *New Frontiers in Fragile X*. UCLID collaborated with the Fragile X Center offering Co-Sponsorship as well as time and staffing resources in support of the conference. UCLID staff developed the design for the Conference brochure as well as the flyer that was distributed. UCLID trainees attended the conference.

Additional collaborative educational and training efforts between the Fragile X Center and UCLID included clinical training on the biological basis of Fragile X syndrome as well as discussing family experiences with the medical community in regards to diagnosis.

- Dr. Noll and Becky Kronk have delivered presentations about Fragile X to specialty departments within CHP including General Academic Pediatrics (GAP), Genetics, and Adolescent Medicine providing these groups with information and support with regards to Fragile X patients.
- The Child Development Unit, where the Fragile X Center is housed, has rotating medical residents, approximately thirty-five (35) per year. Each month these rotating residents are provided the opportunity to participate in the Fragile X Center evaluations. The residents are also given a list of recent, peer reviewed research articles as references to prepare for their experience. Pre and post visit conferences are held to discuss the experience and provide additional didactic information.

State

- Dr. Noll has continued contact with Mr. William Parker in Harrisburg. The Parkers (William and Debra) are interested in establishing a parent support network in Pennsylvania as well as securing funding sources for FX clinical services. Dr. Noll has been working with this family to facilitate their goals and ensure that the CHP clinic is providing necessary support.

Ongoing Goals

- Staff from the Fragile X Center will continue the relationship with Dr. Randi Hagerman from the MIND Institute with the intent to collaborate further in joint research endeavors.
- Dr. Noll and Becky Kronk will continue to serve on the newly formed Network Consortium representing the Children's Hospital of Pgh Fragile X Center.
- The Children's Hospital of Pittsburgh Fragile X Website will be enhanced with two additional sections. A medical section designed to provide information and address questions for professionals, Physicians, CRNP's, etc., is being developed. Additionally we are developing a section on Education that will contain helpful information parents as well as educators of children with Fragile X syndrome.

Objective 3: To develop a patient registry and data base for FX syndrome patients and their families.

- The Fragile X Center established a Research Registry for children who are followed in the Center. With the informed consent from the child or the parent/guardian of the child, current, and future medical record information can be placed into the Research Registry. By placing the medical record information of many patients into a research registry, researchers will be able to review and study the medical records of many individuals and conduct research studies directed at increasing knowledge and answering questions about Fragile X syndrome. 83% of patients seen in the Center are enrolled in the Research Registry; the remaining 17% have expressed an interest in the registry and pending the return of their consent form will also be enrolled.
- Becky Kronk has collaborated with Dr. Don Bailey Research Professor at the University of North Carolina, Director of the Frank Graham Porter (FPG) Child Development Institute, and Distinguished Fellow of Research Triangle Institute (RTI) in preparation for a sleep study to investigate potential linkages between daily bedtime routines, evening fluctuations in parent mood, and sleep patterns for a sample of children with Fragile X.
- Having secured IRB approval, the Fragile X Center has undertaken a sleep study focusing on sleep/wake schedules and sleep patterns in home settings, as well as parent mood. This study will investigate potential linkages between sleep and functional quality of life for families and children. It will examine sleep/wake schedules and sleep patterns in natural home settings across a representative sample of youth with Fragile X through the use of wrist-worn activity monitors ("actigraphs") which allow quantification of sleep patterns in natural home environments; the accuracy of this approach will be validated by concurrently conducting state-of-art laboratory-based polysomnography in a subset of subjects who will wear actigraphs while undergoing EEG sleep studies in our laboratory.

Enrollment in the sleep study is open to children between 3 years and 17 years, 11 months, either full or partial mutation. Families local to the Fragile X Center of Children's Hospital of Pittsburgh are being recruited through the Fragile X Center Research Registry. Additionally inclusion in the sleep study has been extended nationally as well as internationally following the dissemination of preliminary information about the study at the 10th International Fragile X Conference meeting in Atlanta, July 2006 as well as subsequent sharing of that information by interested families on Fragile X syndrome support group list serves. Interest has been expressed from families across the contiguous United States, Canada, Europe, and Southeast Asia. The anticipated sample size for this research study is 185 participants. To date 120 participants are enrolled in the study.

- The Fragile X Center is piloting a project using a web-link that will enable our caregivers and teachers of patients seen in the Fragile X Center to access, complete and submit assessment forms online. These assessment forms can then be downloaded for long-term data storages. This system will allow us to get data instantly from other facilities and off-site clients and research participants.
- With the ongoing growth of the Center, the establishment of our Research Registry and our current Sleep Research as well as plans for future research endeavors, the Fragile X Center contracted with a vendor to build a database that would provide a secure and more robust means of entering and tracking demographic, clinical, neuro cognitive, and research data. With this more refined database we will be able to better track the frequency of the disease and specific symptoms with the goal of guiding future treatment. It will provide us with a means for tracking Fragile X patients seen in the Center both during and post treatment. The system, intended for actual patient care and evaluation as well as for research, will enable us to extract data for reporting or research purposes and will guide future treatment through evidence based medicine.

Ongoing Goals:

- To hire a ½ time Research Assistant who will administer IQ and behavioral assessments and collect developmental, psychometric, and behavioral data from our Fragile X patients and their families.
- To facilitate inclusion of our families in ongoing clinical research programs for individuals with FX syndrome. This would be made possible by increases in the number of individuals with FX syndrome served by the clinic.
- To disseminate information about existing research studies, endorsed, and supported, in progress at other institutions to increase the fund of knowledge about FX syndrome.

Objective 4: To establish a basic science research laboratory.

- A search committee of Dr. Perlmutter, PI, Chair of Pediatrics, Dr. Robert Noll, Chief of Child Development Unit, Dr. Jerry Vockley, Chief of Genetics, Dr. Nina Schor, Chief of Neurology, and Dr. Ron Dahl, WPIC, continues its search for a senior scientist.

REPORTABLE OUTCOMES

There have been no publications in referred journals or grant applications this year. A website has been established and a Children's Hospital of Pittsburgh brochure for Fragile X has been developed.

CONCLUSIONS

The CHP Fragile X Syndrome Center is continuing to emerge as an entity gaining recognition locally and nationally while addressing the needs of families and children with a diagnosis of FX syndrome.